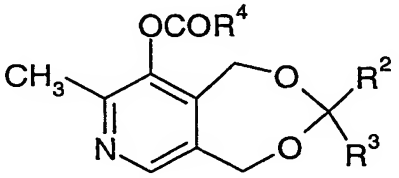
Claims

1. A process for manufacturing a 3-unsubstituted, 3-monosubstituted or 3,3-disubstituted 9-acyloxy-1,5-dihydro-8-methylpyrido[3,4-e][1,3]dioxepin of the general formula

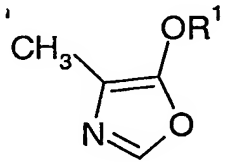


I

wherein each of R^2 and R^3, independently, signifies hydrogen, C_{1-4}-alkyl, C_{2-4}-alkenyl, phenyl-C_{1-4}-alkyl or phenyl, or R^2 and R^3 together with the carbon atom to which they are attached signify C_4- to C_6-cycloalkylidene,
and R^4 signifies C_{1-4}-alkyl or C_{1-4}-haloalkyl,

and optionally for manufacturing pyridoxine,

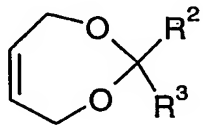
characterized by performing an addition reaction between a 4-methyl-5-alkoxy-oxazole of the general formula



II

wherein R^1 signifies C_{1-4}-alkyl,

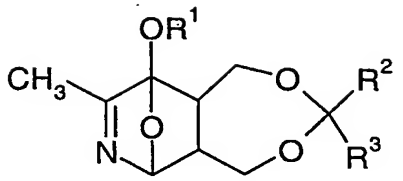
and a 2-unsubstituted, 2-monosubstituted or 2,2-disubstituted 4,7-dihydro-(1,3)-dioxepin of the general formula



III

wherein R^2 and R^3 have the above-mentioned significances,

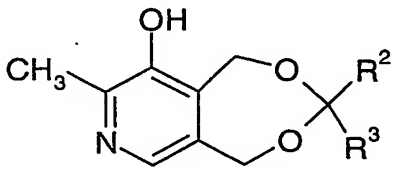
in the substantial absence of a solvent and a catalyst to give a product mixture consisting essentially of the appropriate Diels-Alder adduct of the general formula



IV

wherein R^1, R^2 and R^3 have the above-mentioned significances,

in a major proportion and the appropriate 3-unsubstituted, 3-monosubstituted or 3,3-disubstituted 1,5-dihydro-8-methylpyrido[3,4-e][1,3]dioxepin-9-ol of the general formula



V

wherein R^2 and R^3 have the above-mentioned significances,

in a minor proportion,

removal of a substantial proportion of the unreacted starting materials of formulae II and III from the product mixture by distillation under reduced pressure,

addition of a substantially anhydrous organic acid to said product mixture and rearrangement of the Diels-Alder adduct of the formula IV present therein to further 3-unsubstituted, 3-monosubstituted or 3,3-disubstituted 1,5-dihydro-8-methylpyrido[3,4-e][1,3]dioxepin-9-ol of the formula V in the presence of said substantially anhydrous organic acid with removal of the generated alkanol R^1OH by distillation under reduced pressure, and

acylation of the resultingly enriched quantity of the methylpyrido[3,4-e][1,3]dioxepin-9-ol of the formula V with an added carboxylic acid anhydride of the general formula

$$(R^4CO)_2O \qquad \text{VI}$$

wherein R^4 has the above-mentioned significance,

to produce the desired 3-unsubstituted, 3-monosubstituted or 3,3-disubstituted 9-acyloxy-1,5-dihydro-8-methylpyrido[3,4-e][1,3]dioxepin of the formula I,

and optionally converting this so-manufactured acylation product of the formula I to pyridoxine by acid hydrolysis for achieving deprotection and deacylation.

2. The process according to claim 1, wherein the starting materials of formulae II and III are 5-ethoxy-4-methyl-oxazole (formula II, wherein R^1 signifies ethyl) and 2-isopropyl-4,7-dihydro-(1,3)-dioxepin (formula III, wherein R^2 signifies hydrogen and R^3 signifies isopropyl), respectively.

3. The process according to claim 1 or claim 2, wherein the process step involving the reaction of the starting materials of formulae II and III is effected at temperatures from about 130°C to about 170°C, preferably from about 145°C to about 160°C.

4. The process according to any one of claims 1 to 3, wherein the molar ratio of the dihydrodioxepin of the formula III to the 4-methyl-5-alkoxy-oxazole of the formula II in the reaction mixture is from about 0.5 : 1 to about 5 : 1, preferably from about 1 : 1 to about 2 : 1.

5. The process according to any one of claims 1 to 4, wherein distillation under reduced pressure for the removal of a substantial proportion of the unreacted starting materials of the formulae II and III from the product mixture obtained after the first step is effected by at a pressure in the range from about 10 mbar (1 kPa) to about 100 mbar (10 kPa), preferably from about 20 mbar (2 kPa) to about 50 mbar (5 kPa), most preferably from about 35 mbar (3.5 kPa) to about 45 mbar (4.5 kPa).

6. The process according to any one of claims 1 to 5, wherein an organic acid with a pKa value of up to about 5, preferably a C_{2-5}-alkanoic acid or a corresponding mono- or multihalogenated C_{2-5}-alkanoic acid, most preferably acetic acid, is used as the substantially anhydrous organic acid for the rearrangement of the Diels-Alder adduct of the formula IV to further 3-unsubstituted, 3-monosubstituted or 3,3-disubstituted 1,5-dihydro-8-methylpyrido[3,4-e][1,3]dioxepin-9-ol of the formula V.

7. The process according to any one of claims 1 to 6, wherein the amount of substantially anhydrous organic acid added for the rearrangement of the Diels-Alder adduct is from about 0.01 to about 2.0 equivalents per equivalent of said adduct, preferably from about 1 to about 1.5 equivalents.

8. The process according to any one of claims 1 to 7, wherein the temperature of the product mixture to which the substantially anhydrous acid is added for the rearrangement of the Diels-Alder adduct is from about 50°C to about 115°C, preferably from about 70°C to about 90°C.

9. The process according to any one of claims 1 to 8, wherein the rearrangement of the Diels-Alder adduct with distillation of the generated alcohol R^1OH is effected at a reduced pressure from about 300 mbar (30 kPa) to about 700 mbar (70 kPa).

10. The process according to any one of claims 1 to 9, wherein the carboxylic acid anhydride used for the acylation of the methylpyrido[3,4-e][1,3]dioxepin-9-ol of the formula V corresponds to the anhydride of the substantially anhydrous acid used in the previous process step, and is preferably acetic anhydride.

11. The process according to any one of claims 1 to10, wherein the amount of carboxylic acid anhydride employed for the acylation is from about 1.05 to about 2 equivalents per equivalent of the methylpyrido[3,4-e][1,3]dioxepin-9-ol to be acylated, preferably from about 1.1 to about 1.5 equivalents.

12. The process according to any one of claims 1 to 11, wherein the temperature at which the acylation is effected is from about 50°C to about 115°C, preferably from about 70°C to about 90°C.

13. The process according to any one of claims 1 to 12, wherein the process is carried out continuously for two or more steps.

14. The process according to any one of claims 1 to 13, wherein the optional final step of converting the so manufactured acylation product of the formula I to pyridoxine is realized by procedures well known in the prior art and, depending on the type of acid involved in the acid hydrolysis, produces pyridoxine in the form of the appropriate acid salt.

15. The process according to claim14, wherein pyridoxine hydrochloride is produced.

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